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Vol. III OCTOBER 1947 No. 11

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Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

Published monthly by the Children's Hospital, 13th and W Sts., Washington, D. C.

Subscription rate is $1.00 per year.

SPECAL REPORT

KERNICTERUS*

A Follow-Up Study of Thirty-Five Erythroblastotic Infants

Ralph Stiller, M.D.

With the advent of more detailed knowledge concerning the pathogenesis and treatment of erythroblastosis fetalis, interest has been focused on the possible untoward effects of a successful therapeutic regimen that may result in a live but helpless infant with kernicterus.

The term "kernicterus" was devised by Schmorl [1] in 1903 in referring to what Orth [1] had called "nuclear jaundice" in 1875. Orth described a primary necrosis of the brain associated with secondary bile staining and degeneration of ganglion cells. In 1907 Bencke summarized the prevailing views concerning the relationship between cerebral injury and kernicterus, and it is of interest that one of these theories, that damage to ganglion cells is caused by ischemia (or trauma), in which area of damage there is a subsequent pigmentation, has gained wide acceptance among present day workers in the field. In 1932 Diamond and his colleagues[2] linked together as a single entity the heretofore separate disease states of icterus gravis, congenital fetal hydrops and congenital anemia of the newborn. The new entity was called "erythroblastosis fetalis." In 1933 Zimmerman and Yannet[3] commented on the association between those children jaundiced by the second day of life who died by the fifth or sixth day with signs of involvement of the central nervous system and others who, after a similarly severe attack of neonatal jaundice, lived, only to show later mental retardation and symptoms associated with injuries to basal ganglions (i.e. spasticity of an extrapyramidal type, athetoid and choreiform movements and emotional instability). They noted that in those cases that showed kernicterus at autopsy there was discernible, on microscopic section, bile pigment in isolated nerve cells in the cerebral and cerebellar cortex as well as in the grossly icteric basal ganglions. And they stated, "an appreciable percentage of cases that reveal the symptom complex of icterus gravis present evidence that may be taken as indicative of involvement of the central nervous system (convulsions, spasticity, irregular respirations, drowsiness, vomiting); of these only a small percentage show kernicterus post mortem."

The same two authors[4] in 1935 reported on a child with a stormy icteric

* Summary of a report which appeared in the American Journal of Diseases of Children, **73**: 651, June 1947. Reprinted with permission of the editors.

course at birth who subsequently lived to the age of 3 years, showing during life signs of diffuse involvement of the central nervous system associated with athetotic movements of the extremities. Microscopic examination of the brain at autopsy showed changes strikingly similar to those of kernicterus, though nuclear staining had not been seen in the gross examination. They again put forward the concept of the clinical diagnosis of kernicterus. De Lange[5] in 1935 showed the lack of relationship between the degree of kernicterus and the amount of damage seen on microscopic section. Levine and Stetson[6] in 1937 implicated an isoimmunization factor in the pathogenesis of erythroblastosis, later proved to be the Rh factor by Landsteiner and Weiner[7]; and with this development began what might be called the modern concept of the disease and its present day therapy. Sobel and Zucker[8] in 1940 reported on a case in which a patient at $3\frac{1}{2}$ years with neuromuscular defects, who had previously had erythroblastosis, died and did not show the usual changes of kernicterus at autopsy, but showed "diffuse changes of a moderate degree scattered throughout the cerebral hemispheres and diencephalon." Leonard[9] in 1945 reviewed 55 cases of erythroblastosis at New York Hospital for the years 1938 to 1944. Nineteen of the patients died in the neonatal period, 5 of them showing kernicterus at autopsy. Of the surviving 36, one shows spasticity and mental retardation attributed to kernicterus. On the other hand, Docter[10] in 1945 reported that of 13 patients with erythroblastosis that survived the neonatal period, five (or 38 per cent) showed manifestations of kernicterus, while 6 of the 7 that died showed this lesion at autopsy.

As to the pathogenesis of kernicterus, recently there has been postulated what might be considered a modern version of one of the possibilities suggested by Bencke in 1907. In a recent article, Weiner [11] has suggested that the agglutinated red cells plug the capillaries of the brain, resulting in anoxemia. The ganglion cells, being most susceptible to short periods of anoxia, die and are then stained by the bile in circulation. This leaves a flexible enough concept to explain,the occurrence of degeneration in other portions of the brain, making it a circumstance dependent on the location of the emboli.

The paper by Docter and one of the cases to be presented here (D. J.) prompted me to undertake a similar survey of all proved cases of erythroblastosis fetalis in the records of Children's Hospital, Washington D.C. with a view to ascertaining the number of living kernicteric children in his group.

METHOD

In any study of this sort, the problem invariably occurs as to which cases to include and which to discard in a series. Culling through all the records

in Children's Hospital from 1920 up to and including Dec. 31, 1945, there were 47 cases that could reasonably be thought to fit the pattern of erythroblastosis. In most there was a presenting complaint of jaundice in the first few days of life, but in some merely one of progressive anemia. Not having an obstetric service, the Children's Hospital of necessity received only patients that were considered too ill to be treated in the surrounding hospitals; consequently most of the children showed a rather clearcut pattern of erythroblastosis. However, many of those prior to 1943 had had no Rh determinations made. Therefore an attempt was made to have the mother and child in these families typed and to ascertain the child's developmental status. Although 10 per cent of patients with erythroblastosis do not fit the Rh pattern, it was felt desirable to omit all such patients from this study, as well as to omit all for whom an adequate follow-up was not obtainable. My criteria, therefore, for inclusion in this series are the typical pattern of an Rh-positive child born of an Rh-negative mother, with the presenting complaint of either neonatal jaundice or anemia.

COMMENT AND REPORT OF CASES

There were 35 patients who fitted these criteria for whom either a clinical follow-up or an autopsy was obtained. Of these 35, four were negro and the rest were white. Six of the 35 have died, and it might be of interest to look at these 6 before passing on to the 29 living with whom this paper is more directly concerned. Only 2 of these 6 showed any cerebral involvement that might be construed as being related to kernicterus. One, a white child, 4 days old, jaundiced since birth, had a palpable liver and a red cell count of 1,900,000. There were 4,000 nucleated red cells per cubic millimeter. The child had several convulsions and died on the day of admission. At autopsy the liver and spleen were enlarged, showing congestion on microscopic section. There were areas of yellow pigmentation scattered throughout the cortex and the brain stem. On fixation, yellow and yellow-green pigment was seen chiefly in the brain stem. Staining of the basal ganglia was not noted.

The second of these two was a premature negro infant weighing 4 pounds (1,814 gm.), who had become jaundiced on the third day and died on the sixth. The red blood cell count was 2,900,000. At autopsy, the significant findings included enlargement of the liver with areas of hemopoiesis and a large congested spleen. There were areas of localized pigmentation in the floor of the fourth ventricle and insula.

Three of the remaining four who died showed no abnormalities of the brain at autopsy. In the last case of the 6 the brain was not examined. It is of interest that one of these three with no pathologic cerebral conditions showed clinical involvement of the central nervous system. This was a

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white child whose jaundice appeared on the second day of life and became rather intense, registering an icteric index of 120. There were 7 previous siblings most of whom were jaundiced at birth, but no detailed history as to severity was obtainable. All 7 were living and well. The liver and spleen were both enlarged in this child and there were 2,700,000 red blood cells. On the third day the child's respirations became gasping in type, and it assumed an opisthotonic position. In this condition it left the hospital after a forty-three day stay, having received four transfusions totaling 320 cc. of blood, some of which may not have been Rh negative. It returned about two weeks later, marasmic in appearance, with thrush. The infant showed opisthotonos, was spastic on the right side and held its mouth open with deviation of the jaw to the right. At autopsy the brain was grossly normal, and sections were reported as showing no signs of kernicterus. There was a generalized engorgement of the cerebral vessels.

These 6 deaths bear out the literature in the lack of correlation between the clinical and the pathologic picture, an observation that has been noted before by Zimmerman and Yannet[3] and de Lange,[5] that none of the cases with evidence of pigmentation of the central nervous system was typical of kernicterus in its classical form is not discouraging, as there is evidence in the literature that the damage need not be in the basal ganglia (de Lange[5] and Sobel[8]).

Twenty-nine of the 35 patients in this series are living. Of these, four have failed to develop normally. There is no history of trauma at birth in any of these four and in the presence of the criteria for erythroblastosis fetalis it is felt that these patients represent a group of surviving kernicteric children. All four of the defective children were recognizably backward before the age of one year, two of them showing signs in the neonatal period. Only 10 of this series were, when last observed, under the age of one year, and it appears highly unlikely that any of the children reported here as developing normally will, as time goes on, show defects attributable to their erythroblastosis. It is of interest, that of the 4 negro children reported on in this series, 3 showed involvement of the central nervous system. Two of them are in the living series, and one among those that came to autopsy showed some cerebral pigmentation.

Case 1—D. J., a 4 day old white girl, was admitted to Children's Hospital with a history of jaundice since birth. The infant was full term, apparently the product of a normal labor and delivery. She was given 60 cc. of plasma intramuscularly and fluids subcutaneously at another institution. She did not take her formula well, and one day before admission she vomited some fresh blood. Physical examination on admission revealed an intensely jaundiced 4 day old mildly dehydrated infant, lying in partial opisthotonos. She had a weak, feeble cry, and the temperature was 102°F. There was a

moderate degree of cyanosis. Respirations were irregular, with prolonged periods of apnea. The fontanelle was not bulging, and there were no meningeal signs. The tip of the spleen was barely palpable and the liver 2 finger breadths below the costal margin. The remainder of the physical examination revealed no abnormality.

The mother had had one previous pregnancy that ended in a 6 month nonviable premature infant. Rh determinations were done and revealed that the patient and the father were Rh positive, the mother Rh negative.

Laboratory data on admission revealed a negative Kahn reaction of blood serum and spinal fluid. Initial blood cell count showed 9.5 gm. of hemoglobin, 3,200,000 erythrocytes and 12,600 leukocytes, with a normal differential count. An occasional nucleated red cell was seen. Other laboratory findings included an immediate direct van den Bergh reaction and a bilirubin content of 6.2 mg. per hundred cubic centimeters. This later dropped to 2.4 mg. per hundred cubic centimeters three weeks after admission. Nonprotein nitrogen in the blood was 36 mg. per hundred cubic centimeters, phosphorus was 4.4 mg. and calcium was 12.4 mg. Prothrombin time was 79 per cent of normal. Urine showed initially 50 mg. of albumin per hundred cubic centimeters and some white blood cells. The stool constantly contained bile.

Roentgenograms of the chest and the long bones did not indicate any pathologic condition.

During a hospital stay of forty-two days, the child's condition gradually improved under a regimen that consisted of oxygen, respiratory stimulants, chemotherapy and transfusions (a total of two transfusions, 140 cc. of Rh-negative blood). The temperature returned to normal on the fifth hospital day and stayed there, although the urine continued to show numerous white blood cells in clumps with albumin values up to 100 mg. for some time after the patient became afebrile. Culture of urine showed Escherichia coli. The hemoglobin ranged from the low point found on admission to over 20 gm., and there were over 5,000,000 red blood cells soon after admission. This was followed by a gradual subsidence to lower levels. Clinically, the jaundice slowly waned. Respirations gradually improved but never became completely regular. Some spasticity of the extremities was noted during the child's hospital stay. In this condition, she was discharged from the hospital with a diagnosis of erythroblastosis fetalis, pyelitis and possible kernicterus.

For the next three months she was seen several times in the dispensary, usually for infections of the upper respiratory tract. There are several scattered notes concerning the child's lethargy, and bilateral strabismus was noticed by one examiner.

At the age of 5 months, the infant was brought to the dispensary with a

history of progressive opisthotonos and spasticity of two and one-half week's duration. Examination at this time revealed, in addition, an absence of light perception and sunken, internally strabismic eyes.

On June 13, 1946, at the age of 6 months, the child was readmitted to the hospital because of a temperature of 105°F. associated with listlessness and stertorous breathing. Physical examination revealed a dehydrated, critically ill white girl, with nuchal rigidity, rapid respirations and a chest filled with numerous coarse and fine moist inspiratory rales. A spinal tap yielded clear fluid under no increase in pressure. Subsequent analysis gave negative results. The red blood cell count was 3,900,000, with 12.5 gm. of hemoglobin and 19,700 leukocytes, of which 48 per cent were polymorphonuclear. The urine initially showed 40 mg. of albumin per hundred cubic centimeters, though subsequently there was none.

The child recovered from its acute infection on a regimen that included sulfadiazine, penicillin and oxygen. However, it continually had trouble with its feedings, aspirating food easily and had transient attacks of cyanosis. There was no improvement in its neurologic status, which remained substantially as it was prior to this acute episode. It was noted that the spasticity was changeable in type, sometimes being more marked in one limb, sometimes in another. Gentle pressure was all that was required to break the spasticity, and it was felt that the picture was more in keeping with disease of the basal ganglia than with involvement of cortex or internal capsule. The cranial nerves were intact except for an internal strabismus bilaterally. The fundi showed snowy white disks. Reflexes were hyperactive and gross sensation response was delayed. It was felt that this neurologic picture could be explained by kernicterus.

Case 2—A. P. was brought to Children's Hospital at the age of 12 days with a referral note from another hospital stating that she had been jaundiced since birth. She had had a transfusion of 85 cc. of blood in the other institution. The mother's delivery had been normal. There were 2 siblings living and well.

On admission the infant was severely icteric, appearing dull and somewhat toxic. The posterior fontanelle was almost closed, while the anterior was open 2 finger breadths. The abdomen was slightly distended, the liver and spleen palpable 3 finger breadths below the costal margin. Laboratory studies revealed that the mother was Rh negative and the child Rh positive. Erythrocytes were 2,700,000 and hemoglobin 8.5 gm. An occasional nucleated red cell was seen on the initial smear. With transfusion therapy, a total of 170 cc. on two separate occasions, the count rose to 4,600,000 red blood cells and 15 gm. of hemoglobin during her hospital stay. Other pertinent laboratory findings included an icteric index of 132 units. The van den Bergh reaction was immediate direct; there was 14 mg. of bilirubin per

hundred cubic centimeters, and the Kahn reaction was negative. The prothrombin time was 80 per cent of normal. The urine was not remarkable except for a positive reaction for bile. Roentgen examination of the long bones showed no pathologic conditions.

The child made an uneventful recovery and with the clearing of the jaundice was discharged after a hospital stay of thirty-one days.

In the months following discharge, the infant was seen in the dispensary at varying times for infections of the upper respiratory tract. At the age of 5 months it was noticed that the anterior fontanelle was bulging slightly, that there was no control of the external ocular muscles and that there was slight spasticity of the right arm. The child was seen in the Neurologic clinic at the age of 6 months, and the following note was made: "She will follow mother with her eyes; not able to hold head up, shows no interest in surroundings, does not play with rattle and moves all extremities well. Dentition is at 5 months." The cranial nerves were intact except for paresis of the right sixth nerve. Tonus was judged to be good. Reflexes were present and equal.

At the age of 17 months she was readmitted to the hospital for a pneumoencephalogram. Physical examination at this admission revealed a quiet child who did not protest manipulation and was unable either to sit up or to hold its head up. Laboratory tests showed a moderate degree of anemia. No abnormality was noted with any urinalysis. Examination of the spinal fluid showed 5 mg. of protein and 25 mg. of sugar per hundred cubic centimeters and 10 leukocytes per cubic millimeter, of which 90 per cent were lymphocytes. Reactions to colloidal gold and Wassermann tests were negative. The pneumoencephalogram was interpreted as showing the ventricular system to be well outlined and dilated throughout, particularly in the third ventricle. There was excessive air over the frontal cortex, possibly indicative of either degeneration or agenesis. She was discharged to be followed in the Neurologic clinic.

At the age of 19 months she could move all extremities and was making unsuccessful attempts to sit up. She was making no attempt to speak.

Case 3—C. S., a 4 day old infant, was admitted to Children's Hospital with a history of jaundice appearing one day after birth. The child was full term, and delivery was normal. The infant had 2 siblings, both normal and not jaundiced at birth.

Physical examination revealed a markedly jaundiced, well developed infant boy. The edge of the liver was palpable 2½ finger breadths below the costal margin. The spleen was not felt. There were some impetiginous lesions in both axillas and behind the ears. Other observations were essentially negative. Rh determinations done on the parents and child revealed an Rh-positive father and child with an Rh-negative mother. Anti-Rh

agglutinins were present in the mother's serum in a dilution of 1 to 128. Laboratory observations after two transfusions of 75 cc. each (Rh-negative blood) revealed 14 gm. of hemoglobin and 4,000,000 erythrocytes. A rare nucleated blood cell was seen on the slide.

The child recovered from the jaundice and left the hospital after a ten day stay. One examiner on two separate occasions noticed some spasticity of the arms.

The follow-up in this case has of necessity been second hand. However, by telephone conversation with the mother and by personal conversation with the child's pediatrician, it has been ascertained that at the age of 16 months he has typical spastic paraplegia, being unable to move about and showing no mental development.

Case 4—M. L. at the age of 5 days was brought to the dispensary of Children's Hospital with a history of sudden onset of jaundice that morning. He was the ninth child of a family of 9, the product of a normal labor. The 8 previous siblings were alive and well. The patient was not very ill and was followed in the dispensary for five days. The Kahn reaction of the blood was negative, there was 14.4 mg. of bilirubin per hundred cubic centimeters (normal 0.1 to 0.5 mg.) and the icterus index was 100 units. The hemoglobin was 11 gm. and erythrocytes 2,600,000. There was a normal differential count. No nucleated red cells were seen.

Fifteen months later the child was admitted to the hospital for an infection of the upper respiratory tract. At this time it was noted that he made numerous purposeless movements of his extremities. He was unable to sit up or walk unaided. Various observers described his expression as "blank," although there was some comment concerning his response to being played with and his ability to recognize and reach for toys. Several different examiners agreed in essence on the presence of choreiform movements and the absence of any other significant neurologic findings. With the exception of some mild respiratory infection the remainder of the physical examination revealed no abnormality. Laboratory studies showed the urine to be normal; there was a moderate degree of anemia and the spinal fluid showed no abnormalities. A pneumoencephalogram showed a considerable increase of air in the sulci that was interpreted as possibly indicating some cortical atrophy.

Rh determinations were made at this time. The patient and his father were Rh-positive and the mother Rh-negative. Subsequent investigation revealed that with the birth of her eighth normal child there was some postpartum bleeding and that the mother received several transfusions, most of which were undoubtedly with Rh-positive blood, as this occurred in 1940. The patient was the first offspring following this incident, and another child

born subsequent to this patient, the mother's tenth, was jaundiced at birth. The patient was discharged from the hospital with the diagnosis of kernicterus.

At present, at the age of 3 years, he can walk with a peculiar ataxic lurching gait. He makes continuous purposeless movements with his extremities and head. In reaching for objects he overshoots, then recovers and manages to grasp what he is after. He appears to be mentally alert, can say about ten words and gets on well with his siblings.

There appears to be no correlation in these cases with regard to the degree of jaundice, the intensity of the anemia, the number of transfusions given and the degree of enlargement of the spleen and the liver. As is to be expected, none of these children were first born. Two of them had two elder siblings and one had one sibling. In 2 cases these were normal children, and in 1 case (D. J.) death was by spontaneous abortion in the sixth month. Of interest is case 4, in which, after 8 previous normal births, the last of which necessitated multiple transfusions of Rh-positive blood, the patient was born; an ensuing child was also erythroblastotic. The family history of this case has been reported previously by Relfe and Adams.[12] Of the 4 cases presented here, 2 showed signs of involvement of the central nervous system in the neonatal period. None of the 25 normal children showed any such involvement. Four out of 29 is not a large enough series from which to draw dogmatic conclusions, but it appears to be not too rash a statement to say that the prognosis must be guarded whenever involvement of the central nervous system, no matter how mild, occurs in a newborn infant with erythroblastosis.

In case 2 (A. P.) there was cortical atrophy in the pneumoencephalogram. Again, in this case, the argument might be advanced that this need not be kernicterus. This is admitted, but in view of the possibility that damage to the brain from erythroblastosis is diffuse and not limited to the basal ganglions, it cannot be disproved. Weiner[11] has stated that "infants with kernicterus occasionally survive, in which case they develop signs of a diffuse neurological disorder of varying severity, usually accompanied by mental deficiency." Unfortunately, no statistics appear to be available for comparison on the incidence of neuromuscular defects in any consecutive series of normal births. It is apparent, however, that 4 out of 29, or 15 per cent is a significant figure.

In the light of these figures, the outlook for an erythroblastotic child is not nearly so hopeless as was implied by Docter.[10] The great majority of those that survive will go on to develop normally. Whether transfusion therapy of an intensive nature should be used for those infants that show some involvement of the central nervous system at birth is another matter,

but obviously, in the light of present knowledge, such treatment could not be withheld, as the definite prognosis for these children is not yet established. It might be well to point out that transfusion therapy is merely substitution therapy, and that in the presence of pronounced damage to the central nervous system death may still supervene in the presence of a normal hemogram. Weiner[13] stated that transfusion therapy in erythroblastosis should not be used indiscriminately, but it should be reserved for those that show a low blood cell count, as it will have no salutary effect and may well be detrimental to those with a normal or high red cell count.

SUMMARY AND CONCLUSIONS

Of 35 patients with erythroblastosis for whom follow-up records were obtainable, 29 are still living and 6 have died. The ratio of white to negro in this series was 31 to 4.

Analysis of the autopsy reports of the 6 deaths failed to show any correlation between the degree of clinical involvement of the central nervous system and the pathologic picture.

Of the 29 living children 4, or 15 per cent, showed signs of involvement of the central nervous system that may be interpreted as evidence of kernicterus. Two of these 4 showed evidence of involvement of the central nervous system in the neonatal period. None of the remaining 25 normal children showed any such neonatal involvement.

Transfusion therapy should be directed against the anemia and is of no value in ameliorating the damage to the brain that has already occurred.

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RHEUMATOID ARTHRITIS WITH ASSOCIATED CARDIAC INVOLVEMENT

Case Report No. 106

Herbert Glick, M.D.

J. W. 47–8939
T. H. 47–7186

Case 1: This $5\frac{1}{2}$ year old white male child was admitted to the Children's Hospital on August 30, 1947 with the chief complaint of persistent fever. The present illness began 6 weeks before admission with sudden onset of high fever followed shortly thereafter by generalized joint pains. The fever would reach its highest peaks in the afternoon and evening and would drop considerably by morning. The mother stated that the joints were tender but the pain was not severe nor was there any redness of the surrounding tissues. A week after the onset of his present illness the patient complained of epigastric pain which seemed to be present only in the afternoon when his temperature started to rise. There was no associated nausea or vomiting at this time. About 3 weeks before admission the child complained of pain in the right axillary region which was associated with respiration. During his present illness, the patient was admitted to the Fredericksburg Hospital where he was treated with penicillin, sulfonamide drugs and streptomycin. The diagnosis at that hospital was rheumatic fever with pleurisy.

The patient became progressively weak, pale and lost weight during his present illness. Two days ago he began complaining of pain along the left side of his neck as well as pain in the left eye. There was an associated edema of the left periorbital tissues. Torticollis of the left side of the neck was also noticed. There was no symptomatology referable to the genito-urinary, gastrointestinal or central nervous system.

Past history revealed that in January, 1946 he had a generalized convulsion lasting 30 minutes; he was hospitalized for two days and made an uneventful recovery. The etiology was not established. In March 1946 he was again hospitalized for 11 weeks because of transitory joint pains with high fever. His discharge diagnosis was rheumatic fever. Since then he had complained of generalized malaise, poor weight gain and irritability. The patient lived on a farm and drank well water and pasteurized milk.

Physical examination revealed a poorly nourished white male who appeared chronically ill. The temperature was 99.6° and the pulse 86. His skin was very pale with a suggestive icteric tinge. No petechiae were seen. The neck revealed a torticollis to the left and any movement caused fairly severe pain. Palpable cervical nodes were present and some periorbital edema of the left eye was noted. The pharynx was slightly

inflamed. Examination of the lungs revealed diminished breath sounds over the right axilla but was otherwise negative. The liver was palpable 4 cm. below the right costal margin, while the spleen was palpable 2 cm. below the left costal margin. The extremities showed considerable wasting. There was tenderness of the right knee and hip and the left wrist on motion but no local redness of the joints was observed. The blood pressure was 90/60 and the heart appeared to be enlarged to the left on percussion. A soft systolic murmur at the base was heard.

The urine was essentially negative. The hemoglobin was 8.5 gms. with 2,800,000 red blood cells; the white cell count was 12,600 with 72% neutrophiles and 28% lymphocytes. One malarial smear was negative. A stool culture and febrile agglutinins were negative. The sedimentation rate was 38 mm. per hour. X-ray examination revealed the heart to be enlarged to the left and there was slight eventration of the left diaphragm (Fig. 1).

Since his first hospitalization and continuing to the present time the patient has run a septic fever with an associated rise in pulse and respirations when the temperature reached its daily afternoon peak of about 104°. His appetite has remained quite poor. He was started on oral sodium salicylate (gr. 5 every 4 hours), local applications of methyl salicylate to the involved joints and codeine as needed. In addition he has also received several transfusions. Improvement in his condition, if any, has been slight.

Case 2: T. H., a 4½ year old white male, was admitted to Children's Hospital on July 12, 1947 with the chief complaints of fever and muscular aches and pains of four days duration. The mother stated that he began to complain of pain in his legs on July 8, 1947 but continued to play that day, had a normal appetite and slept well. The following day he continued to have pains in his legs and started to run a fever. He had difficulty sitting up and walking and shortly thereafter he became quite irritable and also began to complain of aches and pains in his arms and back. A local physician considered the symptoms to be referable to an upper respiratory infection and prescribed some "fever tablets." He was seen 2 days later by another physician who prescribed sulfadiazine for acute tonsillitis. However, the symptoms persisted and in addition he began to vomit; hence the sulfadiazine was discontinued and the boy hospitalized.

He was born in St. Joseph's Hospital, Omaha, Nebraska, weighing nine pounds at birth and was the product of a 9 months gestation and a normal labor and delivery. He was breast fed and received an adequate vitamin intake. There had not been any previous illness, hospitalization or operations and he had been immunized against diphtheria and pertussis.

The family history was not revealing. There were only the parents and one sibling and no history of familial or hereditary disease.

The physical examination revealed a rather acutely ill white boy with

slight nuchal rigidity who refused to turn his head to either side. The tonsils were enlarged and inflamed and the pharynx was also injected. The eyes, ears, nose, heart and lungs were essentially negative. The abdomen was tender to palpation but it was not distended and there were no masses or rigidity. The liver, kidneys and spleen were not palpable. The hamstrings were tight and the muscles of both lower extremities were tender.

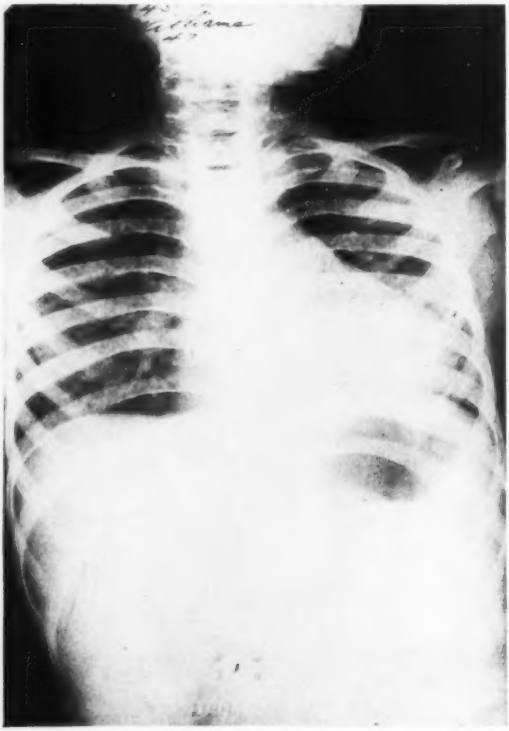

FIG. 1. J. W. Note the enlarged cardiac silhouette with a straight left border and fuzzy cardio-phrenic angles suggestive of pericarditis with some effusion.

The Kernig and Brudzinskis were positive and the Babinski negative. The provisional admission diagnosis was acute pharyngo-tonsillitis and/or poliomyelitis.

About 10 days after admission the middle joint of the middle finger of the right hand became enlarged but there was no heat, tenderness or limitation of function. At this time, the liver and spleen were noted to be enlarged for the first time.

The boy continued to run a fever and was given only symptomatic and supportive therapy in the form of bed rest, vitamins, iron and blood transfusions. He was finally discharged on August 4, 1947 without a definite diagnosis being made and still running a low grade intermittent fever. The spleen had continued to enlarge until it was quite readily palpable about 3 cm. below the left costal margin.

In view of the persistence of fever and weakness at home, the child was admitted to the Harriet Lane Home on August 9, 1947. At that time he appeared chronically ill with fever, lassitude, evidence of weight loss and a generalized pallor. The heart was normal in size and there were no murmurs but the rate was 140. A firm spleen was palpable but the liver did not seem to be enlarged. There was a slight soft swelling of both wrists. They were not acutely tender and passive movement did seem to give rise to some pain. There was swelling also of the right middle and left index fingers. The knees looked a trifle full but definite swelling could not be demonstrated and no tenderness was elicited. Neurological examination was negative. Many laboratory tests were done which were essentially non-revealing. While there he received symptomatic treatment and two transfusions to correct the anemia. He was discharged on September 1, 1947 and returned home. On the following day he developed slight substernal pain and dyspnea. The pain was relieved somewhat by the application of a hot water bottle over his anterior chest and the dyspnea was relieved by propping the patient up on a pillow. The substernal pain and dyspnea progressively increased in severity and on the day prior to his readmission, audible inspiratory and expiratory wheezing was present. He was re-admitted to Children's Hospital on September 4, 1947.

Physical examination at this time revealed an acutely ill, very pale and dyspneic child propped up in bed. His temperature was 102°, pulse 130 and the skin was clammy but there was no cyanosis. The conjunctivae and nail beds were pale. The blood pressure was 102/48. The pulse rate was regular but rapid and of fairly good quality. The heart was markedly enlarged to the right and left on percussion and an equivocal soft systolic murmur was present. The chest was clear to percussion and auscultation. There was voluntary rigidity of the entire abdomen. The liver edge was palpable 3 finger breadths below the right costal margin and was tender; the spleen was similarly palpable and tender. The extremities were similar to the findings described at the Harriet Lane Home and no edema was noted. A provisional diagnosis of congestive failure associated with rheumatoid arthritis was made.

X-ray on admission revealed a markedly dilated heart (Fig. 2) and fluoroscopic examination the following day revealed a definitely enlarged heart with pericardial effusion. The venous pressure was 160 mm. He was placed in an oxygen tent on the evening of admission and full scale digital-

ization was started. On the following day he was markedly improved with considerable diminution in the degree of substernal pain, dyspnea and apprehension. Dr. Walsh saw him in consultation on this day. He has continued to show gradual improvement without remissions. The oxygen tent was discontinued within 48 hours after admission and he has been

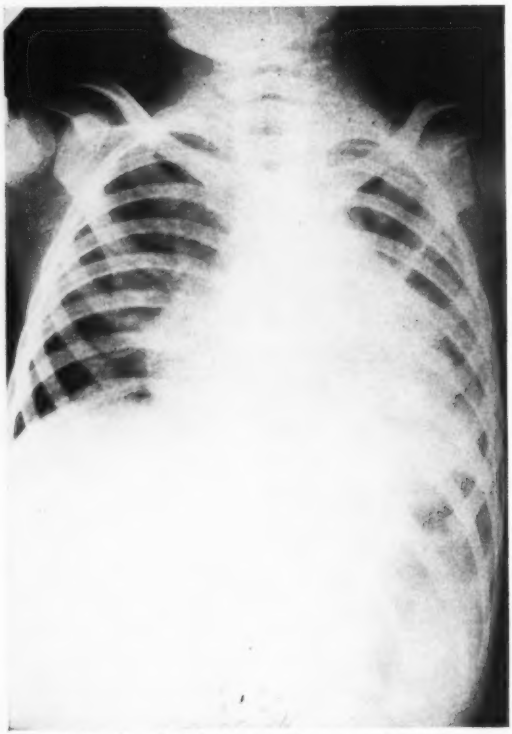

FIG. 2. T. H. Uniformly dilated heart with parenchymal congestion characteristic of heart failure.

receiving maintenance doses of digitalis. He was given a blood transfusion to help correct a fairly marked anemia and is receiving an adequate general diet with added nourishment plus parenteral injections of vitamins B and C.

DISCUSSION

Richard Todd, M.D.: My remarks will be limited to the first child who was admitted on my service. This child shows the characteristic pose of rheumatoid arthritis with his chin drawn down to his chest and resting on

his hand. The neck is the only part of him that is painful at the present time and I think it was noted that it started two weeks before admission. In March 1946 when he had his first bout, his neck became involved, the chin resting on the sternum, and during the 11 weeks of illness he was unable to move it. It has never entirely loosened up. He has not shown the characteristic manifestations of finger joint involvement. His knees have been involved and seemed to bear the brunt of the infection last year and were greatly involved during the present illness. You can see to what extent the second toe is involved; it is not tender but is red and the periarticular tissues are thickened. There is generalized glandular enlargement and the spleen is palpable about one finger breadth below the costal margin. During the one and one half years of illness his chief complaints have been referable to the abdomen. A barium enema showed a redundant colon, a finding which is not too uncommon in these cases. He seems to fit into the category of rheumatoid arthritides which are given the name Still's disease.

The onset was at the age of 4 years and he has had generalized adenopathy, enlarged spleen and anemia. It seems that these cases always look anemic whether they are or not. The skin felt cool to touch which is characteristic and the surface temperature was somewhat lowered. He has the polyarthritis of Still's disease with symmetrical swelling of both knees and wrists and one toe on each foot. He has run a high sedimentation rate of around 40 which is also characteristic. The activity of the disease seems to be in proportion to the sedimentation rate.

Since the etiology is not known, the treatment of Still's disease is symptomatic. The temperature runs a septic course and does not respond to sulfonamides, penicillin or streptomycin. Occasionally it has been associated with a chronic infection due to some focus. The only possible offenders noted were the tonsils and the adenoids which are always suspect. Their removal, however, does not seem to help much. Autogenous vaccines have been of little benefit although I think they are worthy of trial if a definite focus can be established. The course indicates a chronic, atrophic arthritis with frequent exacerbations which have to be treated symptomatically. When the fever subsides, steps should be taken to avoid deformity. The joints become stiff due to fibrous tissue formation and degeneration of cartilage and this can go on to permanent deformity. In the intermission between attacks, physiotherapy and orthopedic care should be instituted to prevent marked deformities.

The symptomatic treatment in this case has been relief of pain with salicylates and codeine. This has been combined with a high caloric diet, adequate vitamins and occasional whole blood transfusions to correct the anemia which is almost invariably present in cases of rheumatoid arthritis.

The cardiac involvement is somewhat unusual. Generally there is no

enlargement of the heart except where there is a pericardial effusion which is occasionally encountered. We are not sure whether or not the pericardial effusion accounts for the enlargement of the heart in this case.

The question of the use of gold parenterally in these cases has been brought up, but there have been some unfortunate accidents following this type of therapy and it does not seem to be too safe although the results in some cases are encouraging.

Robert H. Detwiler, M.D.: This little fellow (Case #2) posed a difficult problem in attempting to establish a diagnosis at the onset. It was only on the day of his first discharge that the diagnosis dawned on me.

The unusual feature was the neurological findings at the onset. The stiff neck, lumbar and quadriceps spasm and weakness and absent knee jerks on one side occurring during the poliomyelitis season presented a picture so much like poliomyelitis that it was hard to get away from this diagnosis.

After reviewing the case again I do not think that we have learned too much which would help us to establish an earlier diagnosis in future cases. I have learned, however, to pay more attention to all the symptoms present in this complex. The mother had to call my attention twice to the swollen middle finger since it was only slightly swollen and non-tender. This was actually the first symptom to point to the diagnosis. When you add up a relatively low red cell count, high sedimentation rate, irregular fever, slight adenopathy, enlarged spleen and finally swollen joints and joint pains you have the early picture of Still's disease.

Preston A. McLendon, M.D.: I saw this child about ten days after admission and the diagnosis of poliomyelitis had been made. At this time there were very few neurological symptoms. In fact, I was not able to demonstrate any evidence of involvement of the central nervous system. The spleen was felt at this time and in view of the history of having recently lived in the country I formulated the impression that this child might have undulant fever. One could not completely eliminate the history of having drunk raw milk. The acute symptoms which this child complained of were not unlike the onset of undulant fever in certain respects. Tests for undulant fever proved to be entirely negative.

In retrospect it is rather interesting that this child showed a symptom complex encountered quite frequently in Still's disease, namely pain and stiffness in the neck. This is apparently due to involvement of the spine in the early stages of the disease where it can not be demonstrated by X-ray as a rule. I do not recall at this time a single case of Still's disease in which cervical pain was not present during its course.

The two cases presented this morning are the only instances that I have encountered having cardiac complications. All patients coming under my observation have, at one time or another, been extremely ill with malaise, high temperature and weakness without cardiac involvement.

Edgar Copeland, M.D.: The significance of cervical spine involvement is a very early sign. I have seldom seen a case in which it was not present. In my experience the onset has been more insidious than in the two cases reported, so much so, that the diagnosis remained in doubt for quite a period. When it comes to therapy, I am in entire agreement with Dr. Todd. The treatment is symptomatic in the complete absence of specific therapy. I have under my care at the present time one such case. In my experience cardiac complications have been very unusual, although such complications have been reported in the literature in a small proportion of cases.

Bernard Walsh, M.D.: Both of these children present several unusual features, but particularly unusual are the evidences of myocarditis as part of the rheumatoid arthritis. The second child presented here, T. H., undoubtedly had heart failure. The increase in the heart size and the evidences of heart failure in this chest film as compared to the chest film taken in July are impressive. It is of interest that this child developed substernal pain on the way home from a Baltimore hospital four days before he entered the hospital here for the second time. During that four day interval he had substernal pain and orthopnea. In addition he seemed to get some relief from his dyspnea when he sat up and leaned forward. Such a position is characteristic in many children with heart failure and in those with cardiac tamponade. When I saw him again, it was at least thirty-six hours after he had entered the hospital, and he was dramatically better in that he no longer had orthopnea and he was able to lie nearly flat without respiratory distress. This marked improvement must have come from the full digitalization which was brought about during the first twenty-four hours of this admission. Certainly we would not expect such improvement in such a short time if the liver enlargement and orthopnea were due to cardiac tamponade.

On the second hospital day Dr. Lattman and I fluoroscoped this patient together. In addition to the moderate cardiac enlargement we were able to see a small amount of pericardial effusion, shown as Dr. Lattman has pointed out by the striking alteration in the size and shape of the pericardial sac in relation to position, that is, when the patient was recumbent there was considerable widening of the pericardial-cardiac contour in the region of the pulmonary artery and left auricular appendage. When the patient was made to assume a nearly erect position, the widening at the base of the heart disappeared only to have considerable widening of the pericardial-cardiac shadow appear just above the diaphragm. While the cardiac pulsations were considerably reduced fluoroscopically in all positions, there did not appear to be a large amount of pericardial fluid. Since the patient was at that time doing very well and has continued to do so, we did not consider it necessary to do a pericardial tap. The electrocardiogram was within

normal range though there was perhaps more right axis deviation than we would expect in a normal child of his habitus.

The other boy, J. W., has very definite enlargement of the cardiac shadow both by x-ray and by fluoroscopic examination. Fluoroscopically there were very poor pulsations seen in the region of the right auricle. This, I believe, is evidence of pericarditis. He has not had any evidence of heart failure. This electrocardiogram is normal.

The process in both of these patients I believe is inflammation of the pericardium and of the myocardium with the latter predominating and causing heart failure in T. H. Pericarditis is occasionally seen as a feature of rheumatoid arthritis but myocarditis wherein it caused cardiac enlargement and heart failure had not occurred in my experience until I saw these two children. It is of interest, however, that in 1941 Baggenstoss and Rosenberg[1] of Mayo Clinic caused considerable excitement in rheumatic circles by describing changes in the heart at autopsy in 14 (56%) of 25 cases of rheumatoid arthritis which so resembled typical features of rheumatic fever that they felt these changes could not be differentiated. I have spoken to two of the outstanding workers in the field of rheumatoid arthritis as to their opinion regarding the histologic changes in the heart in patients with rheumatoid arthritis. These men declared they had no explanation and were considerably puzzled by the apparent similarity between rheumatic fever and rheumatoid arthritis as reported by Baggenstoss and Rosenberg. Clinically there are few similarities between rheumatoid arthritis and rheumatic fever and the incidence of diagnosable rheumatic heart disease in a large series of patients with rheumatoid arthritis is certainly less than 10%. The incidence of rheumatoid arthritis in those with rheumatic heart disease is probably a fraction of 1%. However, the cardiac picture exhibited by these two children may well have some relationship to the histologic changes in the rheumatoid arthritis patients described by Baggenstoss and Rosenberg.

The onset of the infection in both of these children is somewhat unusual. The illness in both began with high fever and in one of them, J. W., daily rises of temperature to 103° or 104° continue. It has been my experience with rheumatic fever that a temperature chart such as this is not seen in rheumatic fever unless there is an overwhelming fatal infection. When one is dealing with a diagnostic problem in a child which is characterized by a temperature of 102° or more every day for more than a week and when one can eliminate the usual causes for fever such as pneumonia, tuberculosis, leukemia and purulent infection, rheumatoid arthritis stands out as one of the most likely diagnoses. Another feature of rheumatoid arthritis that sharply differentiates it from rheumatic fever is the characteristic joint change as shown by both of these patients. The involved joints here are

boggy, swollen, but not particularly hot and are not exquisitely tender. The involved joints can be handled without great complaint on the part of the patient. Joints swollen because of rheumatic fever can seldom be handled and as a rule are exquisitely tender. Furthermore a joint swollen because of rheumatic fever does not remain swollen for more than a few days, whereas in rheumatoid arthritis the joints remain swollen with few exceptions for several weeks at least. The x-ray does not reveal significant changes in the joints of rheumatic fever, and in fact infrequently show significant changes in the affected joints in rheumatoid arthritis until the joints have been involved for many weeks.

In the management of these patients, symptomatic and supportive therapy as indicated by Drs. Todd and Detwiler comes first. Good physiotherapy is also of great importance, and this should be carried out under the direction of the physician by a competent and well trained therapist as soon as the most acute part of the joint symptoms has subsided. This is of the greatest importance in preventing a high degree of ankylosis of the joints and consequent crippling. Gold therapy has passed the experimental stage but it continues to carry some risk and in the average case it need not be considered. It may have to be thought of more seriously in these patients later.

Because of the striking neuromuscular symptoms suggesting poliomyelitis at the onset of T. H.'s illness, it is of interest to note that Morrison, Short, Ludwig, and Schwab[2] have recently shown inflammatory lesions in the peripheral nerves and muscles in patients with rheumatoid arthritis. These changes were demonstrated by electromyographic and histologic techniques.

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TICK PARALYSIS

A Report of Two Cases

Martin F. Randolph, M.D.

B. M. B. 47-6318
C. W. 46-6924

Prior to 1938 all reported cases of tick paralysis in human beings in this country had been located in the far western states—Montana, Idaho, Oregon and Wyoming—regions in which the wood tick Dermacentor andersoni is indigenous. In 1938 Robinson and Canal[1] reported a case in Georgia. This was the first case reported in the east and the first case of tick paralysis following the bite of Dermacentor variabilis, a tick which had not previously been known to cause paralysis in children. Since Robinow's article 12 more cases have been reported in the east—in Georgia[4], South Carolina[3], North Carolina[5], Texas[6], New York[7] and Kentucky[8]. Following is a report of two cases occurring in Arlington and Leesburg, Virginia respectively that were studied and treated in Children's Hospital.

B. M. B., a 3½ year old white female, was admitted to this hospital on June 19, 1947. She was perfectly well until the morning of admission when she awoke and was unable to stand and fell to the floor. She was able to move her hands and arms but not as freely as usual. The sensorium was clear; she experienced no unusual lethargy or drowsiness and had no convulsion or tremors. She had orange juice for breakfast and had no difficulty in swallowing. The patient vomited once on the way to the hospital. When asked if the child had been bitten by ticks, the mother replied "no."

The child was born at term after a normal spontaneous delivery. Birth weight was 7½ pounds. There was no known neonatal icterus, cyanosis, paralysis or convulsions. Developmental history was normal. The only illness the child had experienced was diarrhea of the newborn for three weeks following birth.

Physical examination on admission revealed a well developed and well nourished, irritable child who was alert and responsive. Temperature, pulse and respirations were normal. The child was unable to stand alone, unable to rise to a sitting position or to sit unsupported. She could walk with assistance with an uncoordinated wide gait and fatigued quickly. Further examination revealed abdominal reflexes, knee jerks and ankle jerks to be absent and biceps and triceps reflexes to be hypotonic. There was nuchal rigidity, no ankle clonus and the Babinski showed bilateral plantar flexion. There was generalized weakness of all extremities, more pronounced in the lower extremities. Two ticks were found imbedded in the left parietal area of the scalp. One was large and engorged. Beneath this

tick was a much smaller tick (probably a nymphal). The remainder of the physical examination was essentially negative.

The tick was removed and sent to Dr. Armstrong of the United States Public Health Service for identification. A spinal tap was entirely negative.

One hour after the tick was removed, the patient responded to pin pricks of the feet with flexion of the extremities; three hours later she sat up unaided but was still unable to stand; four and a half hours later the child stood up and began walking; twenty-four hours after removal of the tick the child was completely well. Neurological examination revealed return of all superficial and deep reflexes and a complete physical examination was entirely negative.

The child was discharged home after a twenty-four hour stay in the hospital.

C. W., a 3 year old white female was admitted to the hospital on August 26, 1946. She awoke the morning of admission and staggered into the hall with knees close together, feet apart complaining of inability to walk. Later in the morning she seemed drowsy and slightly disoriented. She had no difficulty in maneuvering her arms or trunk or in holding up her head. She had no dysarthria or dysphagia and no complaints of pain. She vomited once. The area in which she lived was tick infested but there was no history of bites.

The patient was the product of an eight months gestation and an uneventful spontaneous labor. Birth weight was 6 pounds. The neonatal period was not remarkable. Measles was the child's only past illness (July 1945). There were three siblings, all well. There were no familial diseases.

Physical examination revealed a well developed and well nourished white female lying quietly in bed. Temperature, pulse and respirations were normal. The child was unable to stand but had a strong and active kick. She attempted to sit up but was unable to do so. Neurological examination showed all deep reflexes to be absent. The abdominal reflexes could not be elicited but the gag reflex was present. The Babinski was bilaterally negative. The upper extremities were ataxic. Examination of the eye grounds revealed the fundi to be hyperemic and blurred; the optic discs were not visualized.

A tick was found imbedded in the left parietal region of the scalp and removed. The remainder of the physical examination was entirely negative.

Laboratory work on admission showed a hemoglobin of 13 grams, white-cell count 3,900 with 46% neutrophiles and 54% lymphocytes. No abnormal red blood cells were noted. The urine was entirely normal. A spinal tap was done on admission. The fluid was clear and under no

increased pressure. Analysis revealed less than one cell per cubic millimeter, protein 5 mg% and sugar 30 mg%. Spinal fluid culture was negative.

There was no progression of paralysis after the tick was removed. Rather the course was one of gradual improvement of her weakness and ataxia.

Three days after admission the patient still had an ataxic gait. Her only subjective complaint was headache on one occasion and this was evidently of mild degree. Her gait slowly improved and her ataxia completely disappeared by the 10th hospital day. Her course was afebrile. She was discharged completely well on the 12th hospital day.

DISCUSSION

In the United States two species of ticks are known to cause paralysis[10]; in the northwest the tick Dermacentor andersoni Stiles and in the east Dermacentor variabilis Say. It is the latter tick that is indicated in the two cases reported above.

The common dog tick Dermacentor variabilis Say has been recovered in the eastern and central states and in California. Its heaviest distribution is reported to be along the Atlantic seabord. The importance of this distribution is self-evident

The pregnant female is the causative agent. The common site of attachment, as in the two cases reported here, is the scalp. However, the tick may be found along the spine, the axilla, inguinal region, under the breasts—areas where it can "hide out" for the incubation period of six to eight days. The tick remains attached to the body for 10 days or less and is said to inject the largest amount of toxin on the 5th or 6th day.[11] This roughly corresponds to the approximate incubation period given by Robinow and quoted above of six to eight days.

Two causes for the paralysis induced in this disease have been postulated: (1) a toxin elaborated in the developing ova of an impregnated female tick and (2) a virus. The latter etiology is held by most authorities as untenable in the light of the prompt recovery following early removal of the tick. Experiments in Australia have shown a toxin to be present in the saliva and eggs[9] and Steinhaus found the toxin associated with eggs of Dermacentor andersoni.[9]

Experimentally, the disease can be produced at any time of the year[10] but in nature, the greatest incidence is in the summer months. The disease is one of infants and children though it has been reported in adults. Girls are affected twice as often as boys probably because in the long hair of the female infant the ticks go undetected by the parents.[10]

The symptomatology, physical signs and clinical course of our two cases typifies those reported in the literature. In general, the child is irritable

and experiences general malaise 12 to 24 hours preceeding the onset of paralysis. Paresthesias and pain of the lower extremities may or may not be complained of. Incoordination of the lower extremities is quickly superceded in a matter of a few hours by symmetrical flaccid paralysis. A rapid progression of a more or less complete symmetrical flaccid paralysis of the Landry type follows, extending upward, involving the arms and neck. Signs of bulbar paralysis—dysphagia, dysarthria, lingual and facial paralysis—make their appearance and the patient may die of respiratory paralysis. This may all transpire in the span of 12 to 24 hours if the tick is not removed, depending on the amount of toxin elaborated by the tick and its point of attachment. Ticks vary greatly in their toxin producing ability; some produce very little. There appears to be a direct relationship between the proximity of the point of attachment of the tick to the central nervous system (e.g. spine, neck) and the length of the incubation period and severity of the paralysis.

On physical examination a flaccid type of paralysis is soon with absent deep and superficial reflexes. The paralysis is bilaterally symmetrical and almost always begins in the lower extremities and ascends. Sensory changes may or may not be present. Cranial nerve involvement, with the lower cranial nerve being involved first, will be found if bulbar paralysis is present. In the absence of bulbar signs, temperature, pulse and respiration is usually within normal limits.

Urinalysis and culture, blood culture and spinal fluid are uniformly negative. There are no significant changes in the white-cell count or differential.[10]

There are few diseases where the treatment is so simple and the results so dramatic. And yet tick paralysis carried with it a prognosis that is uniformly fatal if the diagnosis is missed. It therefore behooves us to have tick paralysis in mind and to make a meticulous search for ticks whenever a case of ascending paralysis presents itself.

With early removal of the tick there follows a rapid clearing of signs and symptoms usually complete in 3 to 4 days. Failure to remove the tick or too late a removal leads, almost always, to death by respiratory paralysis. In removing the tick, care should be taken that all of the "head" with its hypostome is removed. It is the opinion of some authorities that symptoms which have failed to disappear after removal of the tick are due to failure to remove all the "head parts."[11]

Methods to facilitate the complete removal of the tick are varied. They consist of the application of ether, chloroform, oil, kerosene or gasoline, heat and even excision of the skin containing the tick.[10] To date there is no effective agent which can be applied to the garments or body to prevent tick attachment.[10]

In those cases where early removal of the tick is effected, no further

treatment is necessary. In those cases where the tick is removed later and bulbar paralysis is present a respirator may be needed as well as mechanical suction to remove the nucous puddled in the pharynx and larynx.

The clinical symptoms, the findings on physical examination, the recovery of engorged ticks and the rapid clearing of symptoms and signs following their removal seems to make certain the diagnosis of tick paralysis in the two cases presented.

SUMMARY

Two cases of tick paralysis are presented in detail together with a discussion of the disease and its treatment. It is urged that tick paralysis be carefully excluded by a diligent search for ticks wherever a case of ascending paralysis of the Landry type presents itself.

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CLINICO–PATHOLOGICAL CONFERENCE

Directed by: Dr. E. Clarence Rice
Assisted by: Dr. Recinos and Dr. Bischoff
By Invitation: Dr. Frederic G. Burke

A 7 year old colored girl was admitted to the Children's Hospital with a ten day history of general malaise, anorexia and weakness. For approximately one week she had had a sore throat, swelling of glands in the neck, fever as high as 102.6° F. and occasional vomiting. During the three or four days before admission she had intermittent pain in the right chest, abdomen and legs. The child was treated conservatively in the dispensary for six days and then admission was advised because of persistent fever and the presence of rales in the chest.

The past history included visits to the dispensary for six years prior to hospitalization. Most of these were for treatment of enuresis. The last note was made eight months preceding this admission. The child had laryngeal diphtheria at three and a half years of age and pertussis at five years. One year before, the patient played with a child who died of tuberculosis two weeks prior to this admission. The family history was noncontributary.

Physical examination revealed a well nourished and well developed child who appeared acutely ill. The temperature was 102° F., pulse 110 and respirations 25. The pharynx was markedly reddened and the tonsils were enlarged. There was moderate cervical glandular enlargement. Fine rales were heard over the left scapular region. The liver and spleen were palpable two finger breadths below the costal margins.

Hemogram on admission and on four subsequent occasions showed a hemoglobin which ranged between 9.5 gms. and 11 gms.%, erythrocytes 2,800,000 to 3,300,000, leucocytes 27,000 to 72,000 with 84% to 90% polymorphonuclears. Smears were positive for sickling and negative for malaria. The icterus index was 33 and the Van den Bergh was immediate and direct. The erythrocyte fragility was normal. A blood culture on the 10th hospital day was negative while the agglutination tests on the 6th and 21st days were negative for typhoid, brucellosis and tularemia. In addition the guinea pig innoculation was negative for tularemia. The serum Kahn and Wassermann were negative. Repeated urinalyses were normal as was a PSP excretion test. The spinal fluid was normal in cellular content, protein and sugar. Throat and sputum cultures were negative. Tuberculin tests including both PPD #1 and #2 as well as O.T. (1/10 mgm.) were considered equivocal. The Schick test was positive.

An x-ray on admission revealed the heart, lungs and thymus to be normal. Ten days later a repeat chest film showed increased prominence of the

perihilar markings. Intravenous urogram suggested an obstruction of the left ureter in the region of the promontory of the sacrum with dilatation of the ureter above. The ureter below the obstruction was displaced laterally suggesting that the ureteral obstruction was due to a pelvic mass.

A repeat x-ray of the chest during the second week showed an obliteration of the right costophrenic angle and pneumonitis above the right diaphragm. The liver shadow was enlarged and a subdiaphragmatic abscess was considered as a possibility roentgenologically. On fluoroscopic examination the right diaphragm was freely movable.

One week later a moderate infiltration was seen throughout the inner third of both lung fields on x-ray and was thought to be due to passive congestion.

The child showed a steadily downhill course. Her temperature varied between 100° and 104° F. and the respiratory rate increased gradually. On one occasion she coughed bloody sputum. She frequently complained of abdominal pain and lost considerable weight. On the 13th hospital day a urological consultation was obtained and it was felt that there was no renal or perirenal pathology. Because a sub-diaphragmatic abscess was suspected a laporatomy was done on the 20th hospital day. The liver was aspirated but no pus was obtained. The ureters appeared normal and the obstruction reported by intravenous urogram was not found. In spite of supportive therapy and blood transfusions the child became more debilitated daily and died on the 28th hospital day.

DISCUSSION

Frederic Gerard Burke, M.D.: There are certain conditions and diseases which might be considered from the data available. A 7 year old colored girl with a history of being ill for 10 days with the general symptoms of toxemia, moderate fever and a sore throat presents a rather generic problem which runs the gamut of mild, moderate and severe illness. The presence of generalized lymphadenopathy with hepatosplenomegaly would limit the diagnostic possibilities to conditions which may involve the reticulo-endothelial and lymphatic systems. Certainly when this child was seen on admission with an essentially negative history, on a percentage basis, the most common likelihood was a chronic lymphadenitis associated with a focus of infection probably located in the nasopharynx. However, upon admission her course was not that of a respiratory infection with possible septicemia; it was a progressively downhill course terminating in death about the 4th week after admission. Therefore let us examine the other factors which were noted after her admission to the hospital.

It is stated that the child had laryngeal diphtheria at the age of $3\frac{1}{2}$ years and yet upon admission it was stated that her Schick test was positive.

Presumably at the time of admission for laryngeal diphtheria the child was treated with antitoxin and yet it is hard to explain why the Schick test was positive. The roentgenologist reports that the right diaphragm was elevated on the x-ray of the chest taken on the 17th day after admission. Diaphragmatic paralysis accompanying diphtheria associated with or without diphtheritic myocarditis is not an unusual complication. This is ruled out, however, on the basis of the fact that there is no mention of an elevated diaphragm on the admission x-ray and she did not have any of the clinical manifestations of diphtheria.

Can tuberculosis be indicted? The evidence would seem to say no. The child had a contact with an active case of tuberculosis. She subsequently had clinical findings in the chest of pulmonic involvement. However, the x-rays of the chest upon admission were negative and subsequent x-rays of the chest while showing bilateral infiltration did not have the appearance of tuberculosis. Furthermore the guinea pig inoculations (presumably of the sputum) did not show evidence of tuberculosis and the tuberculin tests were equivocal. While it is true that overwhelming miliary involvement of the lungs with seeding into the various organs occasionally does occur without any corresponding x-ray evidence, in such a case I would expect the meninges to be involved and give a tell tale sign on spinal fluid examination. The spinal fluid was normal. I therefore believe tuberculosis remains a very limited possibility.

This child had marked enlargement of the liver with some liver damage. She had a microcytic hypochromic type of anemia with an elevation of her icterus index. The Van den Bergh would indicate that it probably was of a hemolytic variety or might indicate parenchymatous destruction with the production of hyperbilirubinemia. The white-cell count is most interesting and I think it is one of the more important points in the differential diagnosis. There are not very many clinical conditions which will produce leukocyte counts ranging up to 72,000 with the vast majority of the cells of the polymorphonuclear variety. Certainly on the basis of the differential examination of the blood, benign infectious lymphocytosis and infectious mononucleosis which would have been seriously considered if the differential slide showed a majority of lymphocytic cells are ruled out by this examination.

How about sickle cell anemia? The smear showed the presence of sickling although the number and amount is not stated; it may be presumed that the child was carrying a sickle cell tendency as do approximately 13% of the colored population. The anemia, jaundice, intermittent pains in the chest, abdomen and legs all could be very nicely explained on the basis of sickle cell anemia. I do not doubt that this child did have sicklemia and may have had a certain degree of sickle cell anemia of long standing enough

to cause this amount of systemic damage that did not have significant cardiac enlargement. If we were to explain the liver enlargement on the basis of sickle cell anemia then we must presume capillary damage in the liver which in itself would not cause jaundice but would be caused by a long standing chronic passive congestion with liver damage on the basis of chronic heart failure due to sickle cell anemia. This evidence is lacking. I do not believe that sicklemia was of any importance in her case. Lupus erythematosus disseminata is exluded on the basis of the marked leukocytosis, the absence of urinary findings, the rapid termination, the absence of skin manifestations and the fact that she is colored, lupus erythematosus disseminata being rare in the colored race.

Rupture of the appendix with abscess formation, phlebothrombosis and multiple abscesses of the liver may be mentioned and excluded on the basis of insufficient evidence. Abdominal pain which was present but was not thought to be of any great significance excludes this condition.

The probability of widespread septicemia of streptococcal or staphylococcal variety could probably best explain all of the findings. Widespread sepsis with infarction of the viscera could account for all of the positive evidence that was present. However, I believe this child was probably ill for a longer period of time than was stated in the protocol. The appearance of hilar regions in the lung x-ray was definitely that of glandular enlargement. Subsequent x-rays of the chest showed fibrous infiltration involving primarily the interstitial tissues.

The early appearance and tremendously rapid enlargement of all the lymph and reticulo-endothelial structures during the period of observation suggest a more malignant background than a septicemia of unexplained origin. Hepatosplenomegaly of marked degree, hilar lymph gland enlargement, probably pelvic lymph gland hypertrophy and generalized peripheral lymphadenopathy associated with a septic course and probable superimposed septicemia would suggest a malignancy of these structures. Despite the rarity of Hodgkin's Disease and lymphosarcoma I believe the presence of the extensive lymphatic involvement, marked leukocytosis, the x-ray evidence, and her rapid downhill course are quite in line with such a diagnosis. Furthermore I do not believe that the diagnosis of septicemia and lymphatic malignancy are mutually exclusive. I believe this child had an overwhelming streptococcic or staphylococcic septicemia possibly superimposed or coexistant with lymphatic malignancy of either the Hodgkin's variety, leukemia or lymphosarcoma.

PATHOLOGICAL DISCUSSION

E. Clarence Rice, M.D.: Dr. Burke's diagnosis is correct. This case illustrates one of the difficulties that the physician may enounter at any time, viz, two diseases affecting the patient at the same time, for this patient

had reticulum cell sarcoma and a hemolytic streptococcus infection, the organism being isolated from all of the serous cavities.

Even at necropsy it was difficult to appraise correctly the pathological changes. Both lungs were bound to the adjacent pleurae by rather dense adhesions and a small amount of serosanguinous fluid was present in each. Both lungs were heavy and were studded with numerous grayish nodules averaging 2 to 3 mm. in diameter. The appearance was not unlike tubercles. Microscopic examination shows the alveoli to be filled with erythrocytes, leucocytes, wandering cells, exfoliated epithelial cells and serum. The nodules are made up of variable sized rounded cells with vesicular nuclei and a moderate amount of cytoplasm. Nucleoli are rather prominent. An abundance of reticulum is present. The nodules are neoplastic and have the typical appearance of reticulum cell sarcoma. The bronchial, mediastinal, retroperitoneal and mesenteric nodes are enlarged and rather hemorrhagic, the normal lymphoid architecture having been replaced by neoplastic tissue similar to that seen in the lung. The pericardial sac showed a fibrinopurulent pericarditis with a typical "bread and butter heart." The heart was somewhat larger than normal, the musculature being rather flabby. Microscopic examination showed some evidence of myocarditis and invasion by neoplastic cells. The peritoneal cavity showed dense adhesions in the region of the incision and the omentum and parietal peritoneum had a beefy red color. Approximately 200 cc. of bloody fluid was present. The omentum was thickened and filled with grayish nodules similar to those seen in the lung. The spleen weighed 470 grams, which is 23 times the normal. The surface was mottled and of variable consistency. Light brown homogenous masses extended or irregularly infiltrated the organ. Microscopic examination revealed a replacement of neoplastic tissue, fibrosis, hemorrhage and degeneration. Blood vessels contained tumor cells.

The liver was adherent to the adjacent peritoneum and the lower border was 8 cm. below the right costal margin. Numerous small nodules were scattered throughout. Microscopically, the polygonal cells have often been replaced by masses of neoplastic cells. A delicate fibrillar structure interlaces setting the neoplastic cells in small groups. A fine reticulum is noted between the individual cells. The head of the pancreas had been replaced by a tumor mass. The kidneys were enlarged and were the sites of neoplasia. Purulent fluid was found in the pelvis of the left kidney. The brain was edematous and microscopically perivascular leucocytic infiltration was observed.

Pathologic Diagnosis: Reticulum cell sarcoma arising in the lymph nodes with generalized metastases; subacute adhesive pleuritis, bilateral, and pericarditis; post-operative laparotomy and peritonitis; acute pyelonephritis, left; and encephalitis.